SL-2 **Designed Probes for Measuring and Controlling DNA Damage Repair**

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Despite exciting progress made recently in precision medicine, several common cancers remain difficult to treat, including lung, colorectal, and pancreatic cancer, which together account for over 200,000 deaths annually in the U.S. A common molecular factor in many of these tumors is high levels of reactive oxygen species (ROS), which leads to oxidative damage in DNA. This frequently results in the formation of 8-oxoguanine (8-OG), which is both toxic and mutagenic. To cope with this damage, tumor cells evolve strategies to support rapid growth, and thus often misregulate the enzymes that combat this damage. Two important cases are MTH1 and OGG1, which remove 8-OG from the nucleotide pool and from DNA itself. We hypothesize that developing approaches to measure and control the activities of these enzymes will provide new and promising strategies for controlling tumor growth. However, until very recently it has been difficult to measure or alter these enzymes' activities.

Here I describe the design of novel and sensitive chemical probes that act as luminescence reporters of the cellular activities of multiple DNA damage surveillance pathways, including MTH1 and OGG1. With collaborators we have used these probes to identify new small-molecule modulators of these pathways, some of the first in their class. We are using the information learned to develop new hypotheses regarding how modulating the activities of these pathways via small molecules can provide biologically important mechanistic data, and potentially clinically useful outcomes, in cancer.

Our aims are to develop new probes to quantify specific repair activities in tumor cells and tissues; to identify and develop new small-molecule modulators of the enzymes; and to test novel biological hypotheses regarding how altering repair activity may suppress tumor growth. We hope that our new molecular tools will be useful to the cancer research community as a whole. Moreover, if successful, our work may lead to new targeted strategies for cancer treatment, and to practical methods for evaluating patients for these therapies.